December 10, 2002

Marian Stanley
Manager, Phthalate Esters Panel
The American Chemistry Council
Phthalate Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Stanley:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Phthalate Esters posted on the ChemRTK HPV Challenge Program Web site on February 20, 2002. I commend the Phthalate Esters Panel for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA COMMENTS ON CHEMICAL RTK HPV CHALLENGE SUBMISSION:
PHTHALATE ESTERS CATEGORY

SUMMARY OF EPA COMMENTS

The sponsor, the Phthalate Esters Panel HPV Testing Group of the American Chemistry Council, submitted a test plan and robust summaries for the Phthalate Esters Category dated December 14, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 20, 2002.

EPA has reviewed this submission and reached the following conclusions:

1. Category Justification. The submitter's rationale for selecting and subdividing the category is reasonable for the purposes of the HPV Challenge Program.

2. Physicochemical Properties and Environmental Fate. The physicochemical, photodegradation, and water stability data provided by the submitter are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide biodegradation data for 8 of the 18 sponsored phthalates and data inputs for its transportation and distribution models.

3. Health Effects. The submitted data are adequate for the purposes of the HPV Challenge Program.

4. Ecological Effects. For the most part, acute and chronic data for the category phthalates are adequate, although missing data elements need to be added to the robust summaries. Three transitional phthalates (dihexyl phthalate, diheptyl phthalate and diisoheptyl phathalate) are inadequately represented by DEHP because their physicochemical properties are sufficiently different from those of DEHP to suggest a chronic aquatic toxicity concern. EPA suggests that the submitter conduct a chronic daphnid test on one of these phthalates.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE PHTHALATE ESTERS CATEGORY CHALLENGE SUBMISSION

General

The submitter presented a thorough and well-written test plan. Although the submitter did not provide robust summaries for all cited studies, those missing were not critical to the overall category assessment.

Category Definition

The submitter proposed a category of 18 single and mixed phthalates whose identities and CAS numbers are listed in the submission. They are broadly defined as 1,2-benzenedicarboxylic acids with side chain esters ranging in carbon chain length from C1 to C13. The phthalates were subdivided into three groups based on their physicochemical and toxicological properties: (1) low molecular weight (LMW) phthalates produced from alcohols with straight-chain carbon backbones of #3, (2) transitional phthalates produced from alcohols with straight-chain carbon backbones of C4-6, and (3) high molecular weight (HMW) phthalates produced from alcohols with straight-chain carbon backbones of $C7 or a ring structure. Supporting data on 10 nonsponsored phthalates are included for the transitional and HMW phthalates. The category definition is clearly stated.

While the category definition is reasonable for the purposes of the HPV Challenge Program, higher tiered test results may alter the category definition in the future.

Category Justification

The submitter based the category on fundamentally similar chemical structures--all members are diesters of phthalic acid–and subdivided the category into three groups based on similar physicochemical and toxicological properties. The rationale for the makeup of the category and each subcategory is reasonable for the purposes of the HPV Challenge Program; however, butyl benzyl phthalate (BBP, CAS No. 85-68-7) and diisooctyl phthalate (DIOP, CAS No. 27554-26-3) should be moved from the transitional subcategory to the HMW subcategory because the former substance has a ring structure and the latter has a C7 backbone.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

The data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and stability in water are adequate for the purposes of the HPV Challenge Program.

Biodegradation. In several cases EPA identified important information not cited by the submitter. Robust summaries need to be submitted for these studies to complete the public record for the category.

The submitter provided adequate data for only three of the 18 HPV chemicals. These are:

(1) Dimethyl phthalate (DMP, CAS No. 131-11-3)
(2) Diethyl phthalate (DEP, CAS No. 84-66-2)
(3) 1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS No. 68515-50-4)

The submitter provided inadequate data for the following chemical:

(4) 1,2-Benzendicarboxylic acid, diundecyl ester (CAS No. 3648-20-2)

The submitter concluded that this chemical is readily biodegradable from the results of a modified Gledhill test. This conclusion is incorrect because the Gledhill test is not a test for ready biodegradation. However, EPA will consider it adequate in combination with information obtained from other sources (river die-away test, Saegar, V.W. and Tucker, E.S.; Appl. Environ. Microbiol. 31:29-34 (1976)).

The submitter provided inadequate data for the following chemical:

(5) Mixed decyl, hexyl, octyl diesters of 1,2-benzenedicarboxylic acid (610P, CAS No. 68648-93-1)

The submitter concluded that this chemical is readily biodegradable from the results of a modified Gledhill test. This conclusion is incorrect because the Gledhill test is not a test for ready biodegradation. However, EPA will consider it adequate in combination with information that EPA obtained for CAS No. 117-84-0 (river die-away test, Ritsema, R et al.; Chemosphere, 18: 2161-2175 (1989)).

The submitter did not provide biodegradation data on the following three chemicals. However, EPA will consider these adequately addressed by extrapolation from data provided on analogues.

(6) 1,2-Benzendicarboxylic acid, diheptyl ester, branched and linear (CAS No. 68515-44-6)
(7) Diisoheptyl phthalate (DIHP, CAS No. 71888-89-6)
(8) 1,2-Benzenedicarboxylic acid, didecyl ester (CAS No. 84-77-5)

The submitter did not provide biodegradation data on the following two chemicals; however, EPA identified adequate data from the sources cited below.

(9) 1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear (CAS No. 111381-90-9) (river die-away study, primary biodegradation; Carson D.B. et at; Aquat. Toxicol. Risk Assess., 13th Vol., ASTM STP, 1096 pp 48-59 (1990)).

(10) 1,2-Benzenedicarboxylic acid, dactyl ester (CAS No. 117-84-0)(river die-away study; Ritsema, R. et al.; Chemosphere, 18:2161-2175 (1989)).

The submitter states on pages 23 and 24 of the test plan that there are adequate data for this endpoint and that additional testing is not required. EPA disagrees. The submitter needs to provide measured ready biodegradation data following OECD Guideline 301 for the following eight chemicals for the reasons given below:

(11) 1,2-Benzenedicarboxylic acid, diisooctyl ester (CAS No. 27554-26-3): The submitter concluded that this chemical is readily biodegradable from the results of a modified Gledhill test. This conclusion is incorrect because the Gledhill test is not a test for ready biodegradation.

(12) 1,2-Benzenedicarboxylic acid, (C7, C9) branched and linear (CAS No. 111381-89-6);
(13) 1,2-Benzenedicarboxylic acid, benzyl C7-C9 branched and linear alkyl esters (CAS No. 68515-40-2);
(14) 1,2-Benzenedicarboxylic acid, di-C11-C14, branched alkyl esters, C13 rich(CAS No. 68515-47-9):

There are no acceptable data for these three chemicals or potential “read across” analogues.

(15) 1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear (CAS No. 68515-45-7)
(16) 1,2-Benzenedicarboxylic acid, di-C9-C11 branched and linear alkyl esters (CAS No. 68515-43-5)
(17) 1,2-Benzenedicarboxylic acid. di(C11) ester, branched and linear (DIUP, CAS No. 85507-79-5)
(18) 1.2-Benzenedicarboxylic acid, (C9, C11) ester, branched and linear (CAS No. 111381-91-0):

There are no acceptable data on these chemicals or on any analogues. The Carson et al. data obtained by EPA for CAS No. 111381-90-9 cannot be applied to these chemicals because the uncertainty of the method used (die-away test) is too great and because of the wide range of alkyl functionality (C7-11) in CAS No. 111381-90-9.

Fugacity. The submitter uses the Level I fugacity model in EQC (version 1.01) to determine the partitioning behavior of the test substances. No details on the model input were provided in the test plan or in the robust summary. Measured physical properties are preferred for this model, and when actual data are available they should be used in place of estimated values. Level III (EPIWIN) modeling results generated by EPA indicate that the transitional and HMW phthalates will be distributed mainly to sediment but also significantly to soil, while the LMW phthalates will be distributed mainly to soil and also significantly to water. These results differ from those calculated by the submitter; their estimations indicate that the HMW and transitional phthalates will be distributed mainly to soil. The sponsor indicates that there are sufficient data for this endpoint based on results from a Level I fugacity model and that additional work is not recommended. Although the HPV Challenge Program accepts Level 1 fugacity modeling to estimate transport/distribution values, the EPA believes that values based on a Level III fugacity model are more realistic and useful for estimating a chemical's fate in the environment on a regional basis.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Although there were some inconsistencies in the submission, data on sponsored phthalates plus data on analogous phthalates satisfy all health effects endpoints for the purposes of the HPV Challenge Program.

Repeated-dose Toxicity. Overall data are adequate for the purposes of the HPV Challenge Program. For di-C9-C11 phthalates, supporting data are on an unidentified analogue. The submitter needs to identify the analog. Another option is to use the adequate repeated-dose data from the di-C9-C11 phthalates reproductive toxicity study.

Genetic Toxicity. Overall data are adequate for the purposes of the HPV Challenge Program. However, for DIOP, the adequacy of a negative mutagenicity assay in bacteria could not be determined from the information provided in the robust summary.

Ecological Effects (fish, invertebrates, and algae)

The submitter provided summaries of studies on some category and analogous chemicals. Some of the submitted data for groups II and III are not reliable because endpoints were tested above the chemical's water solubility, and test durations (acute) were too short for chemicals whose calculated log Kow is > 4.2. Only acute studies tested close to the chemicals' water solubility were considered key studies by EPA and commented on for data adequacy. Testing was performed for both branched and linear forms of the transitional and HMW phthalates. The submitter should discuss whether or not differences in toxicity are expected between these forms.

Fish, Invertebrates, and Algae. Acute and chronic toxicity data are adequate for one or more category phthalates in each of the three subdivisions except for three transitional phthalates. Because the calculated log Kow values for DHP, diheptyl phthalate, and diisoheptyl phthalate are more than one log unit lower than that for the analogue DEHP, chronic toxicity may be observed. EPA suggests that one of these transitional phthalates undergo a chronic daphnid test. The submitter may want to do a water solubility test

first to identify the most water-soluble chemical for optimum test design. If a carrier is used, the carrier concentration should be #100 mg/L; however, an emulsifier should not be used. The test should be conducted under flow-through conditions using mean measured concentrations.

The submitter indicated that the use of solvent in the algal tests made them invalid. EPA considers the use of solvent to enhance chemical solubility acceptable as long as the solvent and the amount follow those specified in the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (http://www.oecd.org./ehs/test/monos.htm). These data may be useful and EPA recommends the submission of robust summaries for these studies.

Specific Comments on the Robust Summaries

Health Effects

Seventy-two robust summaries were reviewed. For each endpoint, summaries were submitted for at least one chemical in each of the three groups. In general, the robust summaries provided sufficient information to evaluate the studies, and only a few contained errors or confusing study descriptions. The quality of the reviewed studies was good, as most were carried out under GLP/OECD or similar guidelines.

The submitter did not provide any health effects data for three HMW phthalates: 610P, didecyl phthalate, and DIUP. In addition, robust summaries were not provided for two transitional analogues, dibutyl phthalate (DBP; CAS No. 84-74-2) and DEHP, although quantitative values for all health effects endpoints were included in Table 3 of the Test Plan. These omissions are especially important as the two analogues are prominent in the Test Plan. Finally, robust summaries were not provided for acute oral toxicity data on DEP, DIOP, and DUP.

Acute toxicity. Sixteen robust summaries were reviewed.

DEP. The submitter needs to provide a robust summary for this endpoint.

Di-n-hexyl phthalate. In the robust summary for the rat acute oral study, the LD50 values need to be converted from mL/kg to mg/kg body weight.

DIOP. The sponsor needs to submit robust summary details from a primary source, rather than a secondary one.

Repeated-dose toxicity. Twelve robust summaries were reviewed.

DMP. A robust summary for a 90-day dermal toxicity study in rabbits was incomplete, but it provided sufficient information to evaluate the study. The original study did not report the doses administered, the strain and sex of rabbit, information on the control group or the frequency or method of treatment. Other omissions included the substance purity, group size, mortality and body weight effects, and precise NOAEL and LOAEL values (kidney and lung effects occurred at the two highest dose levels, but the summary only specified the highest dose). The study pre-dated GLP and OECD guidelines. Despite reporting deficiencies, the study appears to be marginally adequate based on the extensive histopathological analysis (7,000 individual tissues examined) and the identification of target organs.

Di-C7-C9 phthalates. Robust summaries of subchronic feeding assays in rats and dogs are inadequate because the analogue used (i.e., the test material) was not defined and only the study NOAEL's were reported.

Genetic Toxicity. Sixteen summaries of gene mutation studies and seven summaries of chromosomal

aberration studies were reviewed.

Diheptyl phthalate. A robust summary for a negative GLP/OECD guideline mutation assay in cultured mouse lymphocytes provided sufficient information to evaluate the study, but it was incomplete. The test material was phthalate mixture 711P (containing no more than 15% diheptyl phthalate), but the summary did not report the compositional basis.

Di-C9-C11 (C10-rich) branched alkyl esters of 1,2-benzenedicarboxylic acid (CAS No. 68515-49-1). A robust summary for a negative mutation assay in *Salmonella typhimurium* did not provide sufficient information to evaluate the study. Omissions included the purity and identity of the test material, the number of replicates, the specific concentrations tested (only a range was reported), the cytotoxic concentration, and positive controls (if used). The study is probably adequate since it followed the standard Ames methods (the basis for OECD guideline 471); negative mutagenicity data are supported by similar results in the mouse lymphoma assay (not reviewed). A robust summary for a negative micronucleus assay in mice exposed by gavage provided sufficient information to evaluate the study, but omitted the group size, gavage vehicle, number of cells examined, positive control use, and the specific procedural modifications. The study followed methods similar to those that were the basis for OECD guideline 474.

Reproductive Toxicity. Nine robust summaries were reviewed. Summaries of multigeneration studies did not always clearly describe results separately for each generation.

DEP. A robust summary for a two-generation (continuous breeding) study in mice omitted the magnitude of the reported changes in organ weight and body weight gain in high-dose animals. The summary was misleading in that it did not report the parental NOAEL for the F1 adults. (The presentation would be less confusing if the results for each generation were reported in separate paragraphs.) The summary was also misleading in stating that the compound did not affect "reproduction" and was "not a reproductive toxicant." It would have been correct to state that the compound did not affect "reproductive performance," but the increased male prostate weight (and right epididymal weight, as reported in the EPA IRIS document for DEP at http://www.epa.gov/iris/subst/0226.htm), suggests that the male reproductive tract is a target of DEP.

BBP. A robust summary for a one-generation study in rats omitted the name of the test material.

Di-n-hexyl phthalate. A robust summary for a 14-week continuous breeding study in rats provided sufficient information to evaluate the study, but it contained some errors and omissions. The summary classed the study as a two- rather than a one-generation study. The summary was incorrect in stating that there were no changes in reproductive organs in high-dose females. Although no microscopic lesions were reported, there was a 31% decrease in uterine weight (NTP-CERHR (2000) Expert Panel review on di-n-hexyl phthalate at http://cerhr.niehs.nih.gov/CERHRchems/index.html).

Di-C8-C10 (C9-rich) branched alkyl esters of 1,2-benzenedicarboxylic acid. A robust summary for one- and two-generation studies in rats identified the highest doses as NOAEL's although toxicity was observed at these levels. Furthermore, since the summary did not clearly report the dose levels for each study, it was not always possible to determine whether reported results referred to the one- or the two-generation study.

Ditridecyl phthalate. A robust summary for a reproductive toxicity study in rats incorrectly reported the lowest test dose as a NOAEL; the live birth index was significantly reduced at that dose. The summary did not specify the basis for identification of paternal and maternal NOAEL's.

Developmental Toxicity. Twelve robust summaries were reviewed.

DEP. A robust summary for a developmental study in rats provided sufficient information to evaluate the study, but it had some omissions and errors. The purity of the test material and the magnitude of the

reductions in food consumption and body weight gain in high dose dams were not reported. The summary was inaccurate in reporting the latter as a reduction in body weight and in reporting the lowest dose tested as the fetal NOAEL. Statistically significant fetal effects (increased incidence in supernumerary ribs) were observed at this dose, thus making it the fetal LOAEL.

Diheptyl phthalate. A robust summary for a developmental study in rats exposed to substance 711P (no more than 15% diheptyl phthalate) provided sufficient information to evaluate the study, but it had some omissions and errors. Omissions included the gestational days of exposure, the percent composition of the test material (including the ~10% C4-C10 substances mentioned on page 18 of the test plan), and the magnitude of changes in body and organ weights.

Diisoheptyl phthalate (CAS No. 71888-89-6). A robust summary for a developmental study in rats provided sufficient information to evaluate the study but was incomplete. Omissions included the purity of the test material and details of the fetal effects noted at the highest dose. The increased liver weights in dams were interpreted as physiologically adaptive, but this may not be justifiable because the liver was not evaluated for histopathology. Therefore, the maternal NOAEL is likely lower than the value assigned in the summary.

Ecological Effects

For fish and invertebrates, all robust summaries lacked the following study details: test substance purity, control response, signs of toxicity/mortality by concentration, 95% confidence limits, and some water chemistry parameters, including pH, amount of carrier solvent, type of carrier, hardness and alkalinity.

For algae, all robust summaries lacked the following study details: test substance purity, number of replicates per concentration, control response, and signs of toxicity per concentration.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.